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Alicia Falkenbach
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January 4, 2006
Date of Signature

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Scott et al.

Examiner: Shanon A. Foley

Filed: June 4, 2001

Art Unit: 1648

Serial No. 09/873,881

For: Recombinant Multivalent Viral Vaccine

37 C.F.R. 1.132 Declaration

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Dr. Joseph Esposito, declare:

1. That I am presently a Senior Advisor on Poxvirus Infections at the Centers for Disease Control in Atlanta, Georgia, and the former Chief, Poxvirus Section of the Centers for Disease Control, and the former Director of the World Health Organization Collaborating Center for Smallpox and Other Poxvirus Infections.

2. That I am an inventor on the above-referenced patent application.

3. That I am familiar with the Office Action dated August 5, 2005, in which claims 1-5 and 8-11 were rejected as being unpatentable over Esposito et al., (U.S. Patent No.

5,266,313), or Lodmel, et al. (*Journal of Virology* (1991) Volume 65, pages 3400-3405), in view of Parrish et al., (*Virology* (1988) Volume 166; pages 293-307; "Parish '88" hereafter) or Parrish (*Virology* (1991) Volume 183; pages 195-205; "Parish '91" hereafter); or Martyn et al., (*Journal of General Virology* (1990) Volume 71 pages 2747-53), or Carlson et al., (*Journal of Virology* (1985) Volume 55; pages 574-582).

4. That, for the following reasons, a recombinant raccoon poxvirus comprising more than one exogenous gene inserted into its thymidine kinase ("TK") site would not be obvious from the cited references.

Esposito et al. and Lodmell et al. (on both of which references I am an author) describe only a monovalent recombinant raccoon poxvirus which expresses a rabies gene. The remaining references only characterize the FPV genome and/or compare it with the genome of the canine parvovirus. Therefore, there would have been no reason to consider making a recombinant raccoon poxvirus expressing both the rabies G protein and FPV VP2 because of these references. However, even if one did conceive of a such a recombinant raccoon poxvirus, there would not be a reasonable expectation that it could be obtained.

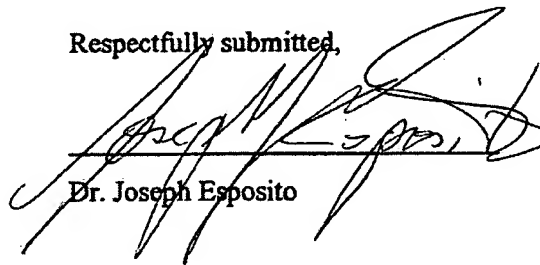
Specifically, the observation that the raccoon poxvirus TK site is non-essential and large relative to the rabies G and FPV V2 genes would not lead to an expectation that a raccoon poxvirus with more than one inserted foreign gene could be constructed. In particular, the non-essential nature of the TK site means that its sequence can be altered without adversely affecting the virus, but inserting foreign genes that must be expressed imposes upon this otherwise "non-essential" region of the genome the requirement that the inserts be properly maintained. However, this is progressively more difficult as more genes are inserted into this site. For example, it has been known since the 1980's that homologous recombination and propagation of recombined viruses is unpredictable and can cause many unexpected changes during recombination of the viral genome and the plasmid which carries the genes to be inserted. This is because homologously recombined poxviruses derive from transient replicative intermediates, which are concatenated genomes, usually in arrangements termed head-to-head (first gene→←first gene), tail-to-tail (last gene→←last gene) and head-to-tail (first gene→←last gene). In the cytoplasm of a host cell, such concatemeric DNA molecules can recombine with each other or recombine upon themselves, and these events

can cause rearrangement or deletion of inserted genes in a process termed "intra-genomic recombination" or "transposition," which can alter or delete foreign genes and/or endogenous viral gene expression elements. Further, in any recombinant vaccine construct, interruption or deletion of the open reading frame of an inserted foreign gene, or a mutation or deletion of the associated poxvirus control elements due to homologous recombination related (or other) events, can lead to a complete lack of gene expression or to expression of aberrant mRNA or protein. Moreover, identifying correctly recombined monovalent virus vaccines requires extensive manual screening of many incorrectly recombined viruses and false positives, and as the number of genes and/or control elements inserted into a recombinant virus increases, so does the likelihood that at least one of the inserted genes or its control elements will be altered in a way which negatively affects expression of the inserted gene. Therefore, at the time the present invention was made, it was unpredictable whether or not two foreign genes could be inserted into the TK site, and it therefore cannot be said that there was a reasonable expectation of success.

5. That all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 101 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued there from.

12/16/05
Date

Respectfully submitted,


Dr. Joseph Esposito

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